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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/994,440	11/26/2001	Melissa K. Carpenter	091/010C	1921

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/994,440	CARPENTER ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/26/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-15 are pending and under current examination.

Election/Restrictions

Applicant's election without traverse of species "a" (Neural Precursor Cells) in the Paper filed 11/03/03 is acknowledged.

Upon further consideration, the Examiner agrees to rejoin the five species of cells recited in the Restriction requirement. As such, claims 1-15 are under current examination.

Information Disclosure Statement

The IDS filed 4/26/02 has been considered and the initialed 1449 accompanies this Office action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 20 of copending Application No. 10/330,873. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to the same subject matter. The instant claim is drawn to methods for obtaining a population of differentiated cells comprising isolating cells from the ICM of a human blastocyst, forming colonies comprising undifferentiated cells from the isolated blastocyst cells, passaging the cells in a culture environment that is essentially free of feeder cells, culturing the passaged cells and differentiating the cultured cells into lineage restricted cells or terminally differentiated cells. The '873 claims are directed to a method of proliferating primate primordial stem [pPS] cells in an undifferentiated state by culturing them on an extracellular matrix with a medium in a growth environment free of feeder cells, further causing or permitting the pPS cells to differentiate. The cells from the ICM of a human blastocyst of claim 1 of the instant application are encompassed by the pPS cells of the '873 claims. Thus, claim 1 of the instant invention are made obvious over the '873 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 7, 8, 10-13 and 15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 19 and 20 of copending Application No. 10/235,094. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of differentiating undifferentiated stem cells isolated from a human blastocyst. The instant claims are drawn to methods for obtaining differentiated cells by isolating cells from the ICM of a human blastocyst, forming colonies comprising undifferentiated cells from the isolated blastocyst cells, passaging and culturing the colonies in an environment that is essentially free of feeder cells, and differentiating the cultured cells into a population comprising lineage restricted or terminally differentiated cells. The instant claims are broader than the '094 claims, which are directed to methods for expanding pluripotent stem cells which have been isolated or propagated from a human blastocyst, culturing the cells in a culture environment containing an extracellular matrix, isotonic culture medium, and fibroblast growth factor, wherein the cells can be differentiated, wherein at least 95% of the cells represent the same germ layer. The '094 claims recite that the culture environment contains an extracellular matrix, isotonic culture medium, and fibroblast growth factor, thus implicitly does not contain feeder cells. As such, the instant claims are made obvious over the '094 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 1 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 33 and 38 of copending Application No. 09/859,291. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of differentiating undifferentiated human ES cells which are cultured in a feeder-free environment. The instant claim is drawn to isolation of cells from the ICM of a human blastocyst, forming colonies comprising undifferentiated cells from the isolated blastocyst cells, passaging and culturing the colonies in an environment that is essentially free of feeder cells, and differentiating the cultured cells into a population comprising lineage restricted or terminally differentiated cells. The '291 claims are directed to isolation of cells from the ICM, forming colonies comprising undifferentiated cells from the isolated blastocyst cells, passaging and culturing the colonies in an environment that is essentially free of feeder cells and then causing the cells to differentiate into a population of differentiated cells. Accordingly, the instant claim is made obvious by the '291 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1 and 4 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of copending Application No. 10/087,473. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of differentiating undifferentiated human ES cells which are cultured in a feeder-free environment, wherein the cells are differentiated by culturing on a solid surface that promotes differentiation. The instant claims are directed to isolation of cells from the ICM of a human blastocyst, forming colonies comprising undifferentiated cells from the isolated blastocyst cells, passaging and culturing the colonies in an environment that is essentially free of feeder cells, and differentiating the cultured cells into a population comprising lineage restricted or terminally differentiated cells. The '473 claim is directed to preparing a suspension of pPS cells from an undifferentiated donor culture that is essentially free of feeder cells, and replating and culturing the suspended cells on a solid surface, where they differentiate without forming embryoid bodies. The isolated cells from the ICM of a human blastocyst of the instant claims are encompassed by the pPS cells of the '473 claim. Thus, the instant claims are made obvious by the '473 claim.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for producing differentiated cells comprising a) isolating cells from the inner cell mass of a human blastocyst, b) forming colonies comprising undifferentiated cells from the isolated blastocyst cells, c) passaging and culturing cells from the colonies in a culture in the absence of feeder cells in a culture environment that comprises an extracellular matrix and a fibroblast-conditioned medium, and d) differentiating the cultured cells into a population comprising lineage restricted cells or terminally differentiated cells, does not reasonably provide enablement for methods for producing differentiated cells by isolation of cell from the ICM of a human blastocyst, forming colonies comprising undifferentiated cells from the isolated blastocyst cells, and passaging and culturing the cells from the colonies in an environment that is essentially free of feeder cells, and differentiating the cultured cells into a population comprising lineage restricted cells or terminally differentiated cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to methods for obtaining a population of differentiated cells, comprising isolating cells from the inner cell mass of a human blastocyst, forming colonies comprising undifferentiated cells from the isolated blastocyst, passaging cells from the colonies into a culture environment that is essentially free of feeder cells, culturing the passaged cells in a culture environment that is essentially free of feeder cells and differentiating the cultured cells into a population comprising lineage restricted cells or terminally differentiated cells.

The specification teaches that feeder cells have been previously used to culture primate pluripotent stem cells, which prevents their differentiation. See p. 3, lines 5-7. The specification teaches methods for growing primate pluripotent stem [pPS] cells *in vitro* without requiring a layer of feeder cells to inhibit differentiation. The specification teaches that the role of feeder cells can be replaced by features in the environment which inhibit differentiation, for example, culture on an extracellular matrix, and by culture in a conditioned media which containing factors that effectively inhibit differentiation. See p. 3, lines 30-33.

The state of the art of culturing of primate embryonic stem cells is such that culturing typically requires the presence of feeder cells. Thomson *et al.* discuss the difficulties in culturing pPS in feeder free conditions. Thomson *et al.* (Reference CN of Applicant's IDS filed 4/26/02) teach the derivation of a cloned cell line from a rhesus monkey that remains undifferentiated when grown on mouse embryonic fibroblast feeder layers, but differentiate or die in the absence of the fibroblasts (see

p. 7844, *Abstract*). Particularly, Thomson *et al.* state that in the absence of the feeder layers, soluble human leukemia inhibitory factor (LIF) fails to prevent the differentiation of the cells, and that the factors that fibroblasts produce to prevent the differentiation of the cells is yet unknown (see p. 7847, 1st column, 2nd paragraph). Thomson *et al.* further state that human inner cell mass-derived cells were cultured in the absence of feeder layers failed to survive beyond 2 passages (see p. 7848, 1st paragraph). The instant specification supports Thomson's finding, stating that, "[T]he role of the feeder cells is replaced by supporting the culture (of pPS cells) on an extracellular matrix and culturing the cells in a conditioned medium." See p. 3, lines 30-31. The specification fails to provide or teach any other conditions in which pPS cells could be grown in feeder-free conditions in the absence of an extracellular matrix, as such, the claimed invention is enabling only for culturing the described pPS cells in the presence of an extracellular matrix.

The specification teaches that conditioned media from several cell lines (MEF, a mouse embryonic fibroblast cell line, NG190, a telomerized mouse embryonic fibroblast cell line, STO, a transformed mouse fibroblast line, BJ 5ta, a telomerized human foreskin fibroblast cell line, and hTERT-RPE, a telomerized human retinal epithelial cell line). The human ES cells were grown on Matrigel in the different conditioned media and it was found that the mEF, NG190, STO and BJ5ta conditioned media supported undifferentiated growth of the hES cells, whereas the RPE conditioned media caused the cells to differentiate within the first

week of culture. See Example 11, and Figure 1. The specification further teaches that medium conditioned using human embryonic fibroblast-like cells derived from the H9 hES cell line was used to culture hES cells and was able to maintain the hES cells in an undifferentiated state. See Example 12, especially, p. 54, lines 36-41. A second human embryonic fibroblast-like cell line [from the H1 cell line] was produced and conditioned medium from these embryonic fibroblasts was used to culture hES cells. The H1-conditioned medium was able to support undifferentiated growth of the hES cells. See Example 13 and Figure 14.

The specification is not found to be enabling for culturing the hES cells in any type of medium to maintain an undifferentiated state. Particularly, because the specification provides sufficient guidance to show that fibroblast-conditioned medium supports undifferentiated growth, and non-fibroblast conditioned medium (human retinal epithelial) causes differentiation of the hES cells. Further, the state of the art of culturing ES cells is unpredictable. Lim *et al.* [**Proteomics**, 2:1187-1203(2002)] teach the proteome analysis of conditioned medium from mouse embryonic fibroblast feeder layers to characterize the environment that supports the growth of undifferentiated human ES cells, and to identify factors critical for their independent growth. See *Abstract.* Lim state that, "Despite many years of using mouse embryonic fibroblast cells as feeder support of human ES cells, it is still not clear what these cells for their clients. The interaction between these two cell types might take place *via* factors secreted into the medium or into extracellular

matrix as well as through membrane-bound proteins." See p. 1188, 1st ¶. Lim teach that by utilizing proteomic analysis, unexpected results identify many known intracellular proteins, and that further analysis using serum-containing medium in the presence of ES cells, and using other cell types for feeder layers will be required. See p. 1203, 1st ¶, #4.

The instant disclosure contemplates utilizing nutrient medium, what which contains, for example, exogenously added factors. See p. 9, lines 34-36. However, specification fails to teach or suggest what particular factors that would be added to a medium that would sufficient to support undifferentiated growth of the ES cells. Furthermore, the state of the art teaches that it would not be predictable that any type of medium would be sufficient to support undifferentiated growth, as evidenced by Lim, who teach that the factors that maintain hES cells in an undifferentiated state, have yet to be identified. Although the specification contemplates utilizing differentiated cells to produce conditioned medium, there are no working examples to show that such medium would be sufficient to maintain hES cells in an undifferentiated state. As specific factors that support undifferentiated growth of hES cells have yet to be identified, it would not be predictable that any media, when used as claimed, would maintain hES cells in an undifferentiated state.

Accordingly, in view of the teachings of the state of the art with regard to the culturing of primate stem cells, the unpredictable nature of culturing undifferentiated primate stem cells in any particular feeder-free condition, the lack

of direction or guidance provided by the specification for culturing the undifferentiated pPS cells under any feeder-free condition, other than the exemplified condition, wherein the culturing of the pPS cells require an extracellular matrix protein and fibroblast-conditioned medium in order to maintain the hES cells in an undifferentiated state, it would have required undue experimentation for one of skill in the art to carry out the claimed methods.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is unclear. The claim recites that the cells are differentiated by withdrawing serum, serum replacement, or a growth factor from the environment. It is unclear if the growth factor is replaced, withdrawn, or how it affects the differentiation.

Conclusion

No claim is allowed. Claims 1-15 are free of the prior art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Note: After January 13, 2004, the Examiner may be reached at (571) 272-0736. If the Examiner is unavailable, inquiries may be directed to Deborah Reynolds, SPE of Art Unit 1632, at (571) 272-0734.

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